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TITLE: Hypo-Fractionated Conformal Radiation Therapy to the Tumor Bed After Segmental Mastectomy

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13. ABSTRACT (Maximum 200 Words)

The current trial tests a regimen of conformal hypo-fractionated radiotherapy (5 fractions) directed to the original tumor bed with margins in a selected subset of post-menopausal women with breast cancer with a very low risk for local recurrence elsewhere in the breast. We are currently reporting the feasibility results and DVH analysis of the first 47 patients accrued. After planning CT is conducted in the prone position the breast tissue and tumor bed are contoured on a 3D planning system and a 2 cm margin added to determine the PTV. A plan is generated to treat the PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95 % isodose surface in 5 fractions over ten days weeks to a total dose of 30 Gy. All patients appeared to tolerate treatment very well. DVH varied based on the position of the original tumor bed and the size of the breast. In most cases it was possible to successfully plan and treat a quadrant of the breast with parallel opposed tangent fields without exceeding 50% of the dose to 50% of the breast volume. We continue accrual as planned, to a total of 99 patients.

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INTRODUCTION:

Since in a selected subset of post-menopausal women with breast cancer there is a very low risk for local recurrence elsewhere in the breast, a regimen of conformal hypo-fractionated radiotherapy (5 fractions in 2 weeks) directed to the original tumor bed with margins, could generates local control rates and cosmetic results equivalent to those achieved by conventional post-operative radiotherapy (30 fractions over 6 weeks) while being much more convenient and economical.

The specific aims of this IDEA grant are:

1. To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers.
2. To explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation.
3. To prospectively assess the role of circulating TGF-β, pre-treatment as a marker for post-treatment fibrosis.
4. To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams

BODY:

An NYU–IRB approved protocol testing the research hypothesis of this study has been actively recruiting patients since October 2000, with independent funding from those allocated by the current award.

The study expects to accrue a total of 99 patients in 3 years.

We are hereby reporting the preliminary results obtained in 47 patients accrued. The first 29 patients have been accrued according to the original DOD approved protocol and consent, since the modifications to the protocol and the consent required by the DOD were minor and have not modified the research component of the trial. The remaining 18 patients have been accrued according to the amended protocol and consent that reflects the minor changes required by the DOD.

With regard to Task 1 and 2 of the approved statement of work: (year 1-4)

"To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers, and to explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation."

At the time of the current report 47 patients have accrued (median age 67.5 years, range: 51 to 88). The median tumor diameter is 1 cm (range 0.2-1.9). Forty-six of the 47 patients completed treatment and are available for follow-up. One patient refused further treatment after 2 fractions for personal reasons, as previously reported. This patient remains in communication with her primary doctor and she is reported to be NED two years later.

All patients appear to tolerate treatment very well with only mild discomfort reported.

The most common acute toxicity was grade 1-2 erythema (21 of 46 patients= 45%) occurring in the treatment portal and fatigue (11 patients), usually manifesting in the second week of treatment. Two patients reported Grade 1-2 nausea. Two patients developed Grade 1 dry desquamation and one patient grade 1 breast edema. Six patients had induration at the surgical scar, pre-dating radiation therapy.
There are 33 patients who have $\geq$ 6 months follow-up. Preliminary assessment of late toxicity, included 12 patients who developed 17 events, including grade 1-2 induration (5 patients), fibrosis (1 patient), breast edema (2 patients), teleangectasia (5 patients0, hyperpigmentation (4 patients).
With a median follow-up of 17 months, preliminary cosmetic grading by the treating physician was "good to excellent" in 24 of 26 patients, "fair" in 2 patients at baseline, which was not changed by the addition or radiation therapy.
Among the 46 patients who have completed treatment no recurrence have occurred: median follow up is 17 months.

During this first phase of the trial we have focused on two tasks:

1) designing a more comfortable and reliable treatment table that can enable geriatric breast cancer patients to comfortably withstand the treatment in prone position.

As a result of a partnership with one of our breast cancer survivor/advocate who is an architect, a new, much more comfortable table for prone imaging and treating was designed (designing and engineering was generously donated by our partner-advocate) and built, as per the attached digital photo (see appendix). The table is now ready for validation and testing to be compared to our previous table (2).

2) developing preliminary **physics data about dose volume histogram (DVH) analysis** in the studied population.

Much of our initial research effort has been spent in studying geometric and anatomic issues of the tested technique and their dosimetric implications.
As described in the original proposal the breast tissue and tumor bed, identified at CT as the post-surgical cavity, are contoured on a 3D planning system (Varian Somavision/CadPlan) and a 2 cm margin added to determine the PTV. A plan was generated in the attempt to treat the entire PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95 % isodose surface in 5 fractions over ten days weeks. to a total dose of 30 Gy.
Planning in the prone position was feasible in 42 patients. Four patients were treated in the supine position (as accepted protocol deviations), 2 patients were unable to tolerate lying in the prone position secondary to paraplegia and 2 patients, the position of the tumor bed was located very lateral and better treated supine. The predominant technique for treatment was a pair of parallel-opposed mini-tangents. This arrangement assured good coverage given the constraints imposed by the PTV and its relationship to the table. For the entire group the volume of breast receiving 30 Gy ranged from 10% to 45%. We found heterogeneity of DVH based on the position of the original tumor bed and the size of the breast. In 12 of the 46 patients, in order to successfully treat the PTV, greater than

50% of the ipsilateral breast volume received >50% of the prescription dose. This was largely dependent on the size of the tumor bed and its location in comparison to the index breast. Doses to the heart and lungs were clinically insignificant.
In conclusion, these preliminary data confirm in that in most cases (35/46) it is possible to successfully plan and treat the PTV with parallel opposed tangent fields without exceeding 50% of the dose to 50% of the breast volume.

Task 3: (year 1-4)
To prospectively assess the role of circulating TGF-β pre-treatment as a marker for post-treatment fibrosis.

As planned, patients were seen once/week during treatment and once two weeks after. Thereafter they will be seen in follow up every 3 months for the first year and every six months for the following five years. At each visit, physical exam to detect clinical recurrence was performed and mammography films (once/year) were reviewed. The data has been regularly collected in the Oracle forms specifically developed for data collection and submitted with the previous annual report.

Task 4: (year 1-2)
To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams.

We had planned to establish the accuracy in target definition by ultrasound imaging and to compare it to CT imaging. Since funding for the acquisition of the US device was obtained only one year ago, only CT imaging was used for the first 47 patients accrued to the trial.
We have just initiated the parallel US evaluation of target volume.

KEY RESEARCH ACCOMPLISHMENTS:

1. feasibility is demonstrated in the first 47 patients
2. dosimetric findings obtained in the first 47 patients appear to confirm our predictions.
3. optimal patient accrual, with an acceptance rate of 94 % among patients who refused the initial recommendation for conventional six weeks of post-segmental mastectomy fractionated radiotherapy

REPORTABLE OUTCOMES:

Since the award was received the study has been presented by the P.I. at three international and three national conferences (all CME approved):

- IV Madrid Breast Cancer Conference: changes in the treatment of breast cancer. Madrid, June 7-9, 2001

- Mayo Clinic Amelia Island Oncology Review Course
  August 15-18, 2001

- Manhattan Breast Cancer Society
  January 17, 2002

- V Madrid Breast Cancer Conference: changes in the treatment of breast cancer.
  Madrid June 11-13, 2003

- American Society for Therapeutic Radiology and Oncology (ASTRO) 45th Annual Meeting, Salt Lake City, Utah, October 19-23, 2003

- Emerging Trends in Adjuvant Therapy of Breast Cancer: 2003 Symposium in New York, October 24-26, 2003

CONCLUSIONS:

The current trial has shown to be feasible and well tolerated. The encountered acceptance rate is 94% in the studied population and the accrual is close to the expected target (44/47).
Preliminary dosimetric findings encourage us to continue especially in view of the excellent tolerability of this approach. Since no local recurrence had occurred after a year of follow up of the first 31 patients, accrual continued as per the Simon stage 2 design. Currently 47 patients have accrued.
Longer follow-up is required for efficacy, cosmesis and to assess the role of circulating TGF-β1 pre-treatment as a marker for post-treatment fibrosis.
The study continues as planned and approved.

REFERENCES:

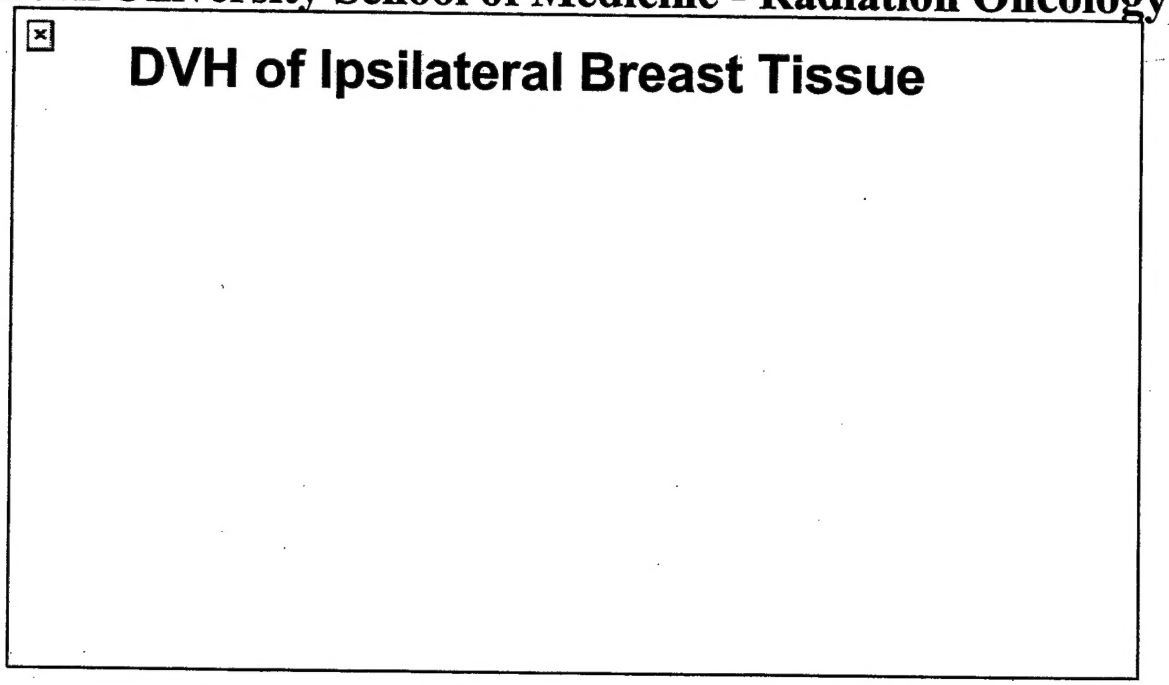
1) Formenti SC, et al Radiology. 2002 Jan;222(1):171-8
2) Joszef G et al Medical Physics 27(5): 1005-10 2000

APPENDICES:

1. updated DVH graph
2. copy of the manuscript
3. Poster of the 47 patients

New York University School of Medicine - Radiation Oncology

DVH of Ipsilateral Breast Tissue



Volume and DVH Summary

	IBV (cc)	CTV (cc)	PTV (cc)	CTV/IBV	PTV/IBV	CTV/PTV	V100	V50
Mean	1124	54	229	5%	22%	21%	26%	47%
Median	1034	35	189	4%	20%	22%	26%	46%
Min	256	7	57	1%	9%	6%	13%	23%
Max	3468	380	1118	22%	55%	46%	45%	75%

IBV: Ipsilateral breast volume **CTV:** tumor bed; clinical target volume **PTV:** planning target volume
V100: volume covered by the 100% isodose surface **V50:** volume covered by the 50% isodose surface

Novel Approaches to Postoperative Radiation Therapy as Part of Breast-Conserving Therapy for Early-Stage Breast Cancer

Minh Tam Truong, Ariel E. Hirsch, Silvia C. Formenti

Abstract

Breast-conserving therapy (BCT) consists of segmental mastectomy followed by postoperative radiation therapy (RT) to the whole breast. At least 6 prospective randomized trials have proven the equivalence of BCT to mastectomy. However, BCT remains underused and, most importantly, a sizable proportion of patients with invasive breast cancer fail to complete the recommended protocol of breast preservation by omitting postoperative RT. The inconvenience of complying with the standard 6-week radiation regimen, which includes approximately 30 daily visits, at least partially explains this lack of adherence. New clinical studies have generated preliminary evidence that more convenient, shorter radiation regimens might reveal equivalence to the current standard. Moreover, the availability of modern technology to deliver and target ionizing radiation by improving homogeneity of radiation dose has made it possible to safely explore the use of greater radiation doses per fraction. Finally, currently ongoing research trials will enable the identification of specific subsets of patients who are likely to be safely treated by partial-breast radiation (instead of radiation to the whole breast) with more accelerated regimens. This article reviews the available data and the current ongoing research on novel RT techniques and fractionation schedules in BCT for early-stage breast cancer.

Clinical Breast Cancer, Vol. 4, No. 4, 253-263, 2003

Key words: Accelerated external-beam radiation therapy, Brachytherapy, Cosmesis, Fibrosis, Partial-breast radiation therapy, Radiation genomics, Telangiectasia

Breast-Conserving Therapy

At least 6 prospective, randomized controlled trials have demonstrated the equivalence of breast-conserving therapy (BCT) to mastectomy.[1-6] Despite level 1 evidence of comparable efficacy to that of mastectomy, BCT remains underused in the United States.[7-12] In 1990, the National Institutes of Health (NIH) Consensus Development Conference concluded that BCT was the appropriate method of treatment for the majority of women with early stage I or II breast cancer.[13] However, this subsequently translated to only a moderate increase in the use of BCT, from 34% to 60% for stage I breast cancer and from 19% to 39% for stage II breast cancer.[14] There appear to be multiple causes for the underuse. The demands of the standard radiation schedule and its perception by referring surgeons and patients probably play a role.

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Generally, radiation therapy (RT) after lumpectomy consists of 4-5 weeks of whole-breast radiation of a total dose of 45-50 Gy in 23-25 fractions, usually followed by a boost of 10-16 Gy in 5-8 fractions to the tumor bed area (Figure 1). The total length of treatment is 5-7 weeks, commonly 6 weeks. Thus, women who choose BCT automatically commit to a regimen of approximately 6 weeks of daily radiation treatments (Monday through Friday) to complete the local management of their breast cancer. For many women, concerns about this commitment are likely to influence the choice for mastectomy instead of breast preservation: only 40%-60% of women who meet criteria for BCT actually undergo the procedure.[14] Studies that have addressed the components of the decision-making choices in women choosing mastectomy suggest that the inconvenience of RT is a factor influencing their decision; concerns arise about the inconvenience, duration of treatment, and travel restrictions associated with the radiation component of breast preservation. The surgeon or primary health care provider also appears to be influential in the process.[15] As a consequence, some surgeons use more stringent criteria than those in published guidelines and recommend mastectomy to their patients based on the perceived difficulties of adhering to a 6-week postoperative regimen.[7] An example of BCT underuse comes from the Arimidex, Tamoxifen, Alone or in Combination trial, in which higher rates

of mastectomy for women who would have otherwise been eligible for BCT had occurred in the United States than in other countries.[16]

In addition to the effect of possible biases of the primary health care provider, distance from RT treatment facilities has also been shown to correlate with patient choice to undergo mastectomy instead of BCT.[17-21] Most importantly, 15%-30% of patients who have actually selected BCT, particularly older patients and those with ≥ 2 comorbid conditions, do not receive postoperative RT.[17,18,22-26] These facts warrant a critical assessment of standard RT and justify the exploration of new radiation regimens.

Radiation Therapy in Breast-Conserving Therapy

Several multivariate analyses have found no patient subgroup with sufficiently low risk of in-breast recurrence (IBR) to avoid treatment with whole-breast external-beam RT as part of the breast-conserving management of breast cancer.[27-29] As a consequence, the last NIH Consensus Statement on this subject (2000) maintained the standard of care for BCT as breast-conserving surgery followed by whole-breast external-beam RT.[30]

Data from pathologic studies justify this recommendation. For instance, in a study of 135 mastectomy specimens of breast cancer from patients theoretically eligible for conservative treatment (≤ 4 cm in size, all pathologic types except invasive lobular carcinoma), it was found that, even with ≥ 1 cm free of tumor beyond the dominant mass, in 11% of cases, tumor was found in the breast beyond 2 cm of distance, thus arguing that surgery alone may not be sufficient.[31]

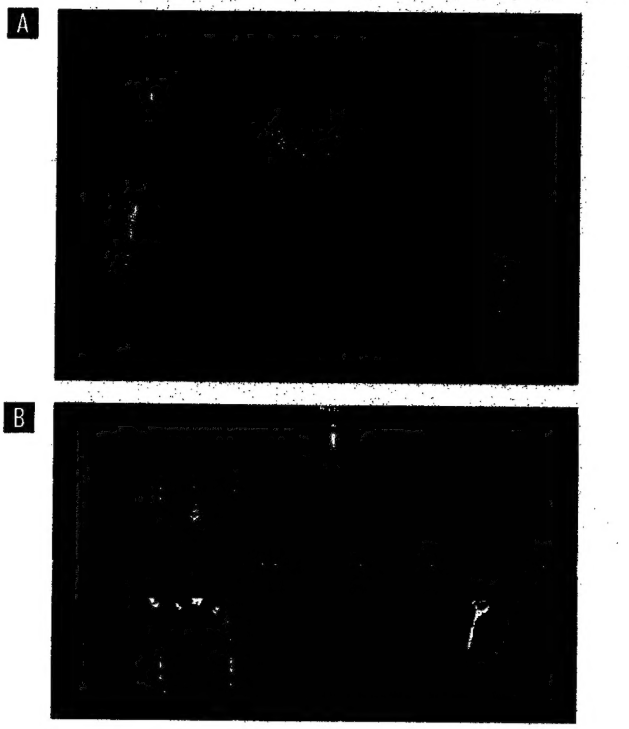
Similar clinical data are available to demonstrate unacceptable risk of recurrence if radiation is omitted. Illustrating this is the experience of the Joint Center for Radiation Therapy in a study that omitted the use of adjuvant radiation after wide excision alone in T1 tumors (median tumor size, 0.9 cm).[32] Eligibility criteria limited study inclusion to carriers of unicentric T1 infiltrating ductal, mucinous, or tubular cancers without extensive intraductal component (EIC) or lymphatic vessel invasion; negative margins of excision measuring ≥ 1 cm; and negative axillary nodes. Despite the stringent eligibility criteria and the fact that 75% of the lesions were mammographically detected (nonpalpable), the study was discontinued prematurely because of unacceptable local recurrence rate: 16% at 56 months of follow-up, or a 3.6% annual rate of local recurrence. The authors concluded that, even in a stringently selected group of patients with early-stage breast cancer, a considerable risk of local recurrence persists after conservative surgery without radiation. Interestingly, most recurrences were at the original tumor site, confirming that the original tumor bed remains the area at the highest risk for recurrence after surgery.

Omission of Radiation Therapy After Quadrantectomy

Recent evidence has emerged that performance of quadrantectomy—a more generous surgical excision than segmental mastectomy, equivalent to a quadrant of the breast—may allow omission of radiation in a selected subset of patients. In a retrospective study of 356 patients > 60 years of age with stage I or II breast cancer treated by quadrantectomy and axillary dissection, the subset of patients with negative lymph nodes and positive receptor status had a locoregional recurrence rate of 3% (median follow-up of 60 months) with or without adjuvant radiation.[33] These findings were confirmed by the results of the Milan III trial, a randomized trial testing the effect of radiation after quadrantectomy.[34] This trial demonstrated that, for women treated by quadrantectomy, as the age of the patient increased, the risk of local recurrence decreased. The difference in the risk for ipsilateral breast recurrence appeared to be particularly high in women ≤ 45 years of age and then tended to decrease with increasing age, with no apparent difference in women > 65 years of age.

In fact, for women ≥ 66 years of age, the local recurrence rate was 4% with or without RT, whereas women < 45 years of age had local recurrence rates of 43% with surgery alone and 9% with surgery and RT. In the group aged 46-55 years, the local recurrence rates were 20.2% without RT versus 5% with RT. In the subset of women aged 56-65 years, the risk was 12.1% without RT versus 2.4% with RT. The authors concluded that women ≤ 55 years of age derive a significant benefit from whole-breast postoperative radiation when quadrantectomy is performed. For women > 65 years of age, quadrantectomy alone is probably adequate.[34]

Figure 1 Digital Reconstruction and Computed Tomography Planning for External-Beam Radiation



(A) Digital reconstruction of a patient's body and projection of tangent beams on the skin surface. **(B)** CT planning for external-beam radiation of a patient in supine position. The normal tissue structures including lung and heart, and tumor and the tangent field are outlined on the digital reconsructed radiograph (top right), axial plane of tangent fields (top left), coronal plane (bottom left), and sagittal plane (bottom right).
Abbreviation: CT = computed tomography

Table 1 Actuarial Results of NSABP B-21 Trial

Treatment	Median Follow-up (Months)	Number of Patients	5-Year IBR	8-Year IBR
Surgery + Tamoxifen + Radiation	87	334	2%	2.8%
Surgery + Placebo + Radiation	86	332	4%	9.3%
Surgery + Tamoxifen	89	334	10.5%	16.5%

Abbreviations: IBR = in-breast recurrence; NSABP = National Surgical Adjuvant Breast and Bowel Project

In North America, quadrantectomy is not commonly performed, and according to a retrospective study of McCready et al, may translate to patients treated with segmental mastectomy or lumpectomy.[35] Local failure rate was 9% at 10 years after lumpectomy alone among patients who were ≥ 65 years of age and had favorable pathologic features including negative nodes, no comedo features, no lymphovascular invasion, and estrogen receptor–positive tumors.

Omission of Radiation Therapy After Segmental Masectomy

The identification of a distinct subset of women who could be safely treated by segmental mastectomy without the addition of RT was the motivation for 2 prospective randomized trials in older women that further addressed the issue of omitting RT in elderly patients. A Canadian randomized trial of women > 50 years of age with T1 or T2 node-negative breast cancer compared tamoxifen alone to tamoxifen and RT.[36] With a median follow-up of 3.4 years among 769 patients (83% with T1 breast cancer), the relapse-free rate in the ipsilateral breast was 94% in the tamoxifen-alone arm, compared with 99.7% in the tamoxifen/RT arm ($P = 0.0009$).

An Intergroup trial conducted by Cancer and Leukemia Group B randomized 647 postmenopausal women ≥ 70 years of age with stage I estrogen receptor–positive breast cancer to tamoxifen versus tamoxifen and RT. With a short follow-up of 28 months, the rate of locoregional failure was very low, 0.9% annually (6 of 319 recurrences in the tamoxifen-alone arm and none in the tamoxifen/RT arm; P value not significant). This study suggests that the benefit derived from RT in this elderly group of patients is very limited as a result of the high incidence of death from other causes. The rate of breast recurrence in the index breast was actually similar to the rate in the contralateral breast.[37]

Could an original tumor size of ≤ 1 cm justify the avoidance of postoperative RT? This was investigated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial, which was limited to women with invasive breast tumors ≤ 1 cm in largest dimension, who had undergone lumpectomy with tumor-free margins at pathology, and who had axillary dissection with negative lymph nodes. Approximately 80% of the women in the NSABP 21 trial were ≥ 50 years of age and 76% of women were postmenopausal.[38] The cumulative incidence of IBR at 8 years was 16.5% with tamoxifen alone, 9.3% with RT and placebo, and 2.8% with the combination of tamoxifen and RT. Distant treatment failures were infrequent and not significantly different among groups ($P = 0.28$). Survival rates in the 3 groups were 93%, 94%, and 93%, respectively ($P = 0.93$). Although NSABP B-21 trial showed that whole-breast external-beam RT significantly reduced the actuarial estimate of incidence of IBR at 8 years, it also demonstrated that IBR continued to occur with time, as demonstrated by the gradual increases at 5 and 8 years of follow-up (Table 1). Protracted observation time to assess IBR is warranted, even in a population of patients with very small primary breast cancers.

Patterns of Local Recurrence After Breast-Conserving Therapy

Results from 5 prospective randomized trials of breast-preserving surgery with or without adjuvant RT have elucidated the geographic patterns of local recurrence after lumpectomy alone and thereby provide the foundation to justify the exploration of partial-breast irradiation (PBI)[2,28,29,38-40] (Table 2[1,2,28,29,40]). In each of these trials, most failures occurred in the tumor bed, raising questions as to the necessity of irradiating the whole breast. For instance, in the NSABP B-06 trial, all recurrences were reported to be within or close to the quadrant of the original tumor.[41] In the study of Liljegren et al, in a more select group than patients from NSABP B-06, 381 patients with unifocal T1 breast cancers (premenopausal and postmenopausal women) were randomized to sector resection with or without radiation.[29,42] Predictably, at 10-year follow-up, significantly higher rates of local recurrences occurred in the arm of patients who underwent segmental mastectomy alone compared with the arm of patients who underwent segmental mastectomy and postoperative RT (24% vs. 8.5% at 10 years). Noticeably, 67% of the recurrences in the surgery-alone arm occurred within the initial tumor bed. A similar geographic pattern of local recurrence has also been demonstrated in other studies.[43,44] The study of Veronesi

Table 2 Prospective Randomized Trials of Breast-Preserving Surgery with or Without Adjuvant RT

Study	Number of Patients	Cancer Size (cm)	Type of Surgery	Local Recurrence with Surgery Alone	Local Recurrence with Surgery + RT	Follow-up (Years)
Fisher et al[1]	1362	4	WE	39%	14%	20
Veronesi et al[2]	567	4	Q	8.8%	2.3%	20
Clark et al[28]	837	4	WE	35%	11%	7.6
Liljegren et al[29]	381	2	SR	24%	8.5%	10
Forrest et al[40]	585	4	WE	24.5%	5.8%	6

Abbreviations: IBR = in-breast recurrence; Q = quadrantectomy; RT = radiation therapy; SR = sector resection; WE = wide excision

et al, which included a more generous surgical operation, a quadrantectomy, had the lowest local recurrence rate, suggesting that surgical removal of more tissue adjacent to the tumor favorably affects local control.[45]

In these randomized trials, the arm of patients who did not undergo RT to the whole breast consistently showed higher recurrence rates and a pattern of recurrences that occurred mostly in the tumor bed. These findings question whether irradiation to the whole breast is necessary and have opened the opportunity to investigate PBI in selected patients with breast cancer treated by BCT.

Challenging the Current Standards for Volume and Dose Fractionation of Breast Irradiation

Although it is clear that the exploration of shorter treatment regimens is warranted, especially in view of the fact that new technology has made it possible to homogeneously deliver radiation treatment while better sparing normal tissue, the optimal fractionation regimen for postoperative breast RT has yet to be defined.

Whole-Breast Radiation: Accelerated Fractionation Regimens

Hypofractionated Accelerated Regimens. Hypofractionation (the delivery of dose fractions substantially larger than the conventional 2 Gy) for breast cancer treatment was common in the 1940s and 1950s and, even though successful in achieving tumor control, was found to leave significantly inferior cosmetic results as a result of severe fibrosis and telangiectasia.[46,47] These late complications resulted from the use of very large fields that included a large proportion of uninvolved skin and tissue surrounding the tumor. Already in 1949, Baclesse had discovered the therapeutic ratio was largely dependent on the field size.[48] He advocated the use of a "sufficient number of contiguous small fields in rotation" as the future for breast cancer RT.

Baillet et al conducted the first prospective randomized trial studying hypofractionated radiation.[49] Patients were randomized to receive either "classical" RT consisting of 45 Gy in 25 fractions over 33 days or hypofractionated radiation consisting of 23 Gy in 4 fractions over 17 days. The first 230 patients randomized were followed for a minimum of 4 years. The 5-year actuarial survival was identical in the 2 arms. The local recurrence rates were 7% (9 of 125) in the hypofractionated radiation group and 5% (5 of 105) in the classical RT group, with no significant difference in local control between treatment arms. The study also detailed complications of each treatment groups including arm lymphedema, fibrosis, and telangiectasia. No statistical difference in the overall rate of complications between the treatment groups was noticed: 23% hypofractionated group versus 19% in the classical group.

Among a number of retrospective reports on shorter whole-breast radiation fractionation schemes, perhaps the most relevant is by Olivotto et al.[50] The regimen used a dose of 44 Gy in 16 fractions in 22 days via tangential fields to the whole breast of 186 women with T1 or T2 pathologically node-negative breast cancer. The 5-year actuarial recurrence rate was 6%, which was comparable with other studies of conventional fractionation (over 6 weeks). Additionally, evaluations of the cosmetic scores were good or excellent in 89% and 96% of cases according to physicians and patients, respectively. Thirteen percent of patients reported mild inframammary telangiectasia at 5-year follow-up.

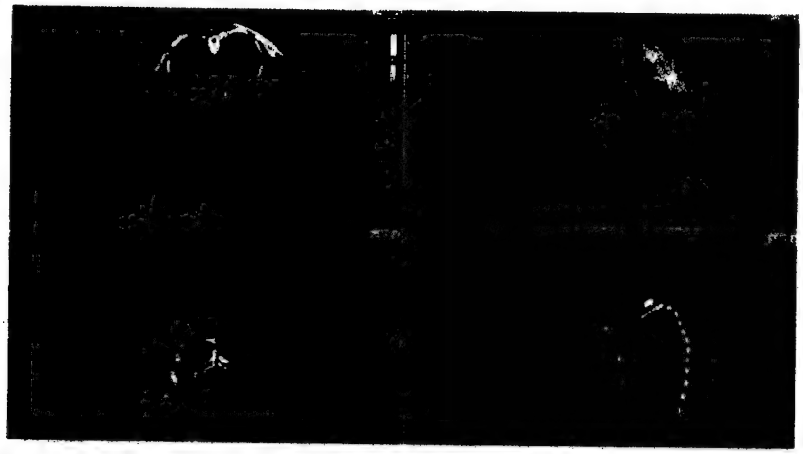
A Canadian retrospective review of a shorter radiation schedule used in patients with breast cancer after lumpectomy provided the preliminary evidence to further explore that hypofractionation schedule.[51] A total of 298 patients were treated with 40 Gy in 16 fractions at 2.5 Gy per day with opposed tangent fields. Median follow-up for this series was 5.5 years. The 5-year actuarial relapse rate was 3.5%, with overall 5-year survival and disease-specific survival rates of 87.8% and 92.1%, respectively. These results were comparable with those derived from historical controls. The regimen appeared sufficiently safe and effective to be prospectively tested in a subsequent phase III trial.

The controlled randomized trial of Whelan et al compared 2 radiation schedules after lumpectomy in women with lymph-node negative breast cancer.[52] The trial included women with T1/2 N0 tumors that were completely excised with negative margins. Between 1993 and 1996, 1234 women were randomly assigned to either the "long" arm of 50 Gy in 25 fractions over 35 days or the "short" arm of 42.5 Gy in 16 fractions over 22 days (2.65 Gy per day). The primary endpoint was the assessment of local control in the treated breast. There were a number of exclusion criteria including breast size (distance of separation ≥ 25 cm), lack of levels 1 and 2 lymph node dissection, and positive margins. At a median follow-up of 69 months, the 5-year local recurrence–free survival rates were 97.2% in the short-RT arm and 96.8% in the long-RT arm. Overall and disease-free survival rates were also equivalent. The incidence of late skin toxicity was low in both arms, with comparable cosmetic outcome. Specifically, the percentages of patients with an excellent or good global cosmetic outcome at 3 years were 76.8% in the short-RT arm and 77.0% in the long-RT arm; the corresponding data at 5 years were 76.8% and 77.4%, respectively. Although this trial represents an important milestone in the investigation of modern RT in breast cancer, more work needs to be done, for instance, to explore how to integrate a boost to the tumor bed in accelerated whole-breast radiation or how to develop a technique that does not exclude patients with large breasts.

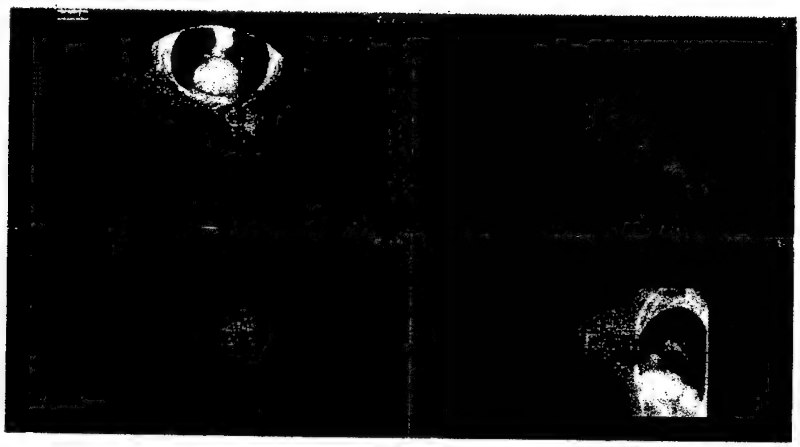
Hypofractionated Nonaccelerated Regimens. In another randomized trial, between 1986 and 1998, 1410 patients with early-stage invasive breast cancer were randomized to 3 different dose fractionation schedules, all delivered over a period of 5 weeks. Of note, although the trial tested hypofractionation, it did not accelerate treatment; rather, overall treatment time remained the same (5 weeks). The 3 schedules were 50 Gy in 25 fractions daily over 5 weeks (2 Gy per fraction), 39 Gy in 13 fractions (3 Gy per fraction), and 42.9 Gy in 13 fractions (3.3 Gy per fraction). The latter 2 schedules are delivered on Monday, Wednesday, Friday, Tuesday, Thursday, etc, 5 times every 2 weeks. Only initial cosmetic results have been reported,[53] and the trial has now been incorporated into the UK Coordinating Committee on Cancer Research breast RT fractionation trial, the Standardization of Breast Radiotherapy Trial, which was closed to accrual in September 2002.

Figure 2 Digital Reconstruction and Computed Tomography Planning in a Prone Position

A Whole-Breast Radiation



B Partial-Breast Radiation



Intensity-Modulated Radiation Therapy

Intensity-modulated RT (IMRT) uses a sophisticated computer-controlled radiation beam delivery method to improve the conformation of the dose distribution to the shape of the tumor. This is achieved with variation of the radiation intensity within each beam, as opposed to the uniform beam intensities used by 3-dimensional (3D) conformal RT. Intensity-modulated RT usually incorporates inverse treatment planning, whereby the user initially specifies the organ dose limits and the desired doses to the target tissues. The computer then generates an optimal plan then adheres to the dose limits specified.

To improve upon the dose delivery achieved by 3D conformal RT using breast wedged tangents, IMRT has been applied to breast RT. Intensity-modulated RT aims to improve the dose to all critical normal tissue structures including the heart and lungs. While current studies of IMRT applied to breast radiotherapy have shown its feasibility,[54-59] long-term data has yet to determine whether this technique translates to an improvement in the late toxicity profile and cosmesis.

Volume-based IMRT first requires outlining the volumes of interest (target and critical organs) and uses specialized computer treatment planning algorithms to generate a plan that optimally balances the conflicting dose constraints to the target and critical organs. The drawbacks of volume-based IMRT are the increased length of time to deliver the treatment and the labor-intensive dosimetric planning, making it difficult to translate IMRT to a large-scale implementation.[54] However, recent studies have shown that more simplified techniques have evolved.[55,56] Chui et al described a practical and simplified technique of delivering IMRT,[55] which requires significantly less "beam-on" time and dosimetric planning than full-fledged volume-based IMRT, which Hong et al originally described.[54] The technique still achieves the desired dose homogeneity when compared with conventional tangents.

Lief et al explored the potential application of IMRT to accelerated breast RT with patients treated in a prone position.[60] This technique involves prescribing a homogeneous dose to the whole breast while a higher dose is delivered to the tumor bed, thereby delivering the equivalent of a concomitant boost (Figure 2A).

Partial-Breast Irradiation

Treatment Volume: Rationale for Partial-Breast Irradiation

Partial-breast irradiation is generally administered to the portion of the breast that includes the tumor bed, plus a surrounding margin. The advantage of PBI is that, by limiting the volume treated, it is theoretically possible to increase the dose per fraction and safely accelerate dose fractionation, allowing patients to undergo a more convenient and possibly more economical radiation regimen as part of BCT. The cost depends on the procedure used. External-beam (3D conformal) accelerated RT costs less because of the decreased number of fractions compared with the standard regimen (5 vs. 30). Conversely, the use of IMRT is likely to increase cost compared with standard tangent treatment. Similarly, PBI delivered by brachytherapy is likely to be more expensive given the costs associated with operating room time, anesthesia, specialized instrumentation, and radiation sources.

Identification of patients who should be excluded from the accrual to these PBI trials because they are likely to either be insufficiently treated by accelerated PBI or are more likely to develop complications when exposed to larger doses per fraction is rapidly evolving. For instance, Holland et al found that tumors associated with EIC were more likely to have carcinoma in the remaining breast than tumors without EIC (74% vs. 42%; $P = 0.00001$), suggesting a role for whole-breast radiation when EIC is present in view of a large subclinical burden in the remaining breast.[61] Another factor

predicting a higher risk of recurrence includes the presence of involved margins of excision.[62,63] Carriers of tumors that lack these features are likely to be better candidates for accelerated PBI trials.

Partial-Breast Radiation Procedures

Currently, the main available methods of delivering PBI are brachytherapy with ≥ 2 plane implants, use of the MammoSite® device, or external-beam radiation with use of 3D conformal RT, IMRT, intraoperative electron beam RT, or stereotactic radiosurgery.

Brachytherapy Techniques. When brachytherapy is used, radiation can be delivered either at a low dose rate (LDR) over 4-5 days or at a high dose rate (HDR) with 8-10 large fractions. The target volume is the tumor bed with margins. Advantages are the established role of brachytherapy techniques and shortened overall treatment time compared with standard 6-week external-beam radiation. The disadvantages are the need for an invasive surgical procedure, the dependence on skills and experience of the radiation oncologist performing the procedure, and the risk of complications derived from dose inhomogeneity within the target volume. Although the results of the initial brachytherapy experience were disappointing, more recent studies with careful quality assurance and accurate patient selection have led to excellent local control rates with these techniques.

A trial by Fentiman et al investigated LDR brachytherapy to a total dose of 55 Gy with use of Iridium 192 and reported an unacceptably high breast recurrence rate of 37% (10 of 27 patients) at a median follow-up of 6 years.[64,65] The investigators attributed the high local recurrence rate to the disproportionate inclusion in this series of younger women with unfavorable tumor characteristics, including median tumor diameter of 3.5 cm in the relapse group, and the presence of lymphovascular invasion, necrosis, positive margins, and involved axillary nodes. Moreover, most women received possibly inadequate implants, with a median number of 9 catheters resulting in treatment to the target volume with insufficient margins.

In a study by Clark et al, HDR brachytherapy delivering a total dose 20-32 Gy was used.[66] The local failure rate was 15.5% (7 of 45 patients) at 18 months.

King et al conducted a prospective phase I/II study of wide-field brachytherapy after segmental mastectomy for selected patients with breast cancer with intraductal or invasive tumors ≤ 4 cm in size, negative inked surgical margins, and ≤ 3 positive axillary nodes using wide-field double-plane ^{192}I brachytherapy implants.[67] Alternating consecutive cohorts of 10 patients were assigned to receive either continuous LDR brachytherapy of 45 Gy to the target volume over 4 days or fractionated HDR brachytherapy of 32 Gy in 8 fractions of 4 Gy each, given twice a day (b.i.d.) over 4 days. A matched-pair analysis with 94 patients who would have met the eligibility criteria for the study but were treated with conventional external-beam RT during the same time period was performed. With a median follow-up of 75 months, the locoregional recurrence rate was 8% (1 breast recurrence and 3 regional nodal recurrences among 51 cases) in the brachytherapy group, compared with 5% in the external-beam RT group (*P* value not significant).

Similar results were reported by Vicini et al, who conducted a retrospective matched-pair analysis of 174 patients with stage I/II infiltrating ductal carcinoma with tumors < 3 cm, negative EIC, negative surgical margins, and < 3 lymph nodes involved.[68] One hundred twenty patients (69%) underwent LDR brachytherapy (50 Gy over 96 hours) and 54 patients (31%) underwent HDR brachytherapy (46 patients received 32 Gy in 8 fractions 6 hours apart and 8 patients received 34 Gy in 10 fractions 6 hours apart). Fifty-two percent of the patients received adjuvant tamoxifen and 11% received adjuvant systemic chemotherapy. At a median follow-up of 36 months, there were no statistically significant differences in the 5-year actuarial rates of ipsilateral breast or locoregional recurrences and no differences in disease-free or overall survival.

Perera et al reported a pilot study of 39 patients who underwent HDR brachytherapy.[69] At a median follow-up of 20 months, 1 local recurrence was reported. Complications of treatment included fat necrosis in 4 patients (10.3%) at the lumpectomy site at 4, 13, and 18 months after implantation.

At a multiinstitutional level, the first preliminary report of Radiation Therapy Oncology Group (RTOG) 95-17 shows promising results.[70] RTOG 95-17 is a phase I/II multiinstitutional trial investigating brachytherapy alone after lumpectomy in 100 patients with tumors ≤ 3 cm excised with inked negative margins. Exclusion criteria were lobular histology, presence of EIC, and ≥ 4 involved nodes. Thirty-three patients were treated with LDR brachytherapy (45 Gy over 3-5 days) and 66 patients were treated with HDR brachytherapy (34 Gy in 10 b.i.d. fractions over 5 days). The target volume was defined as 2 cm beyond the lumpectomy cavity peripherally and 1 cm superficial and deep. At a median follow-up of 2.7 years (0.6-4.4 years), the incidences of grade III toxicity were 9% in LDR-treated patients and 2% in HDR-treated patients. It was noted that patients who received chemotherapy had a substantially increased risk of complications compared with patients who did not: 55% with LDR brachytherapy and 14% with HDR brachytherapy. Among patients who did not undergo chemotherapy, grade III toxicity occurred in no patients receiving LDR brachytherapy and 4% of patients in the HDR brachytherapy group. Furthermore, acute toxicities related to the surgical procedure in addition to radiation toxicity included breast edema, hematoma, arm edema cellulitis, skin necrosis, abscess formation, wound dehiscence, and breast distortion.[70]

Wazer et al described clinically evident fat necrosis after HDR brachytherapy alone using remote afterloading in 8 of 30 patients (27%) at a median of 7.5 months after the procedure.[71,72] The incidence of fat necrosis appeared to be related to the increased number of source dwell positions and the volume of implant receiving fractional doses of 340, 510, and 680 cGy. A dose–volume effect was shown such that use of implants of larger volume necessitated lowering the fractional dose in order to minimize the risk of late complications. This emphasizes the importance of the volume of tissue being irradiated and its consequences on the probability of complications.

Keisch et al recently reported the multicenter preliminary experience in 54 patients who were implanted with the MammoSite balloon breast brachytherapy applicator.[73] The reason to investigate this device is its potential to be a more

Table 3 Results of Sole LDR and HDR Brachytherapy to the Tumor Bed

Study	No. of Patients	Median Follow-up (Months)	Dose Fractionation	Total Dose (Gy)	Local Recurrence Rate	Good to Excellent Cosmetic Result
HDR Brachytherapy						
Clark et al[66]	45	18	10 Gy × 2 7 Gy × 4 6 Gy × 6	20 28 36	15.5%	95%
King et al[67]	26	75*	4 Gy × 8	32	2%*	75%*
Vicini et al[68]	46 8	36*	4 Gy × 8 3.4 Gy × 10	32 34	0	80%*
Perera et al[69]	39	20	3.72 Gy × 10	37.2	2.6%	–
Kuske et al[70]	66	32*	3.4 Gy × 10	34	–	–
Wazer et al[72]	32	33	3.4 Gy × 10	34	3%	75%
Keisch et al[73]	43	1	3.4 Gy × 10	34	–	88%
Polgar et al (Phase II)[75]	8 37	57	4.33 Gy × 7 5.2 Gy × 7	30.3 36.4	4.4%	97.8%
Polgar et al (Phase III)[75]	63	30	5.2 Gy × 7	36.4	0	–
LDR Brachytherapy						
Fentiman et al[65]	27	72	45 cGy/hour	55	37%	83%
King et al[67]	27	75*	40 cGy/hour	55	2%*	75%*
Vicini et al[68]	120	36*	52 cGy/hour	50	0	80%*
Kuske et al[70]	33	32*	45 cGy/hour	45	–	–

*LDR and HDR combined.
Abbreviations: HDR = high dose rate; LDR = low dose rate

reproducible method of breast brachytherapy that is less dependent on the surgical implant technique. This prospective pilot study tested the use of the MammoSite balloon breast applicator using ^{192}I HDR brachytherapy as a sole radiation modality after lumpectomy in women > 45 years of age with stage I breast cancers with negative pathologic margins. The study design consisted of a total dose of 34 Gy, delivered in 10 fractions b.i.d. for 5 days, prescribed to 1 cm from the applicator surface. Only 43 of the 54 patients were found to be eligible for this technique. MammoSite balloon delivery was not feasible in cases of inadequate balloon-to-skin distance, excessive surgical cavity size, poor balloon conformance, or poor skin-to-device spacing. Complications included seromas (3 of 43) and abscess formation (1 of 43). Dose–volume histogram (DVH) analysis of the MammoSite device appeared to compare its use favorably with catheter-based breast brachytherapy. Generally, the MammoSite device treated a larger volume than its interstitial brachytherapy counterparts. The investigators hypothesized that by following the dose–volume cutoffs, fat necrosis would be unlikely to occur, but this prediction warrants further clinical confirmation.

There have been a number of phase I/II trials of brachytherapy as the sole radiation modality to the breast.[69,72,74] Polgar et al reported the first randomized phase III trial of sole HDR brachytherapy compared with whole-breast RT, with a median follow-up of 30 months.[75] Eligible patients were those with unifocal tumors of stage pT1 N0 or pN0-1a. Pure ductal or lobular pT1s tumors, invasive lobular tumors, and presence of EIC were criteria for exclusion. Initially, 45 patients were enrolled onto a phase I/II study of brachytherapy alone with use of interstitial HDR implants consisting of 7 fractions of 4.33 Gy (n = 8) and 7 fractions of 5.2 Gy (n = 37) delivered to the tumor bed. Based on the results of the initial phase I and II study, 126 patients were further randomized to receive 50 Gy whole-breast RT (n = 63) or brachytherapy alone (n = 63). The dose regimen consisted of either 7 fractions of 5.2 Gy HDR brachytherapy (n = 46) or 50 Gy wide-field electron radiation (n = 17). The locoregional control rate was 100% in each arm and the 3-year probabilities of cancer-specific and relapse-free survival were 98.1% and 98.4% in the whole-breast radiation group and 100% and 94.4% in the brachytherapy group, respectively. There was no significant difference in outcome or in the incidence of radiation side effects between the 2 treatment arms; however, because of the small number of patients in each arm, it may not be powered to detect a difference. More prospective randomized data will be required to confirm this. Table 3 summarizes HDR and LDR brachytherapy as sole radiation modality after breast-conserving surgery.[65-70,72,73,75]

The current experience using brachytherapy for PBI is promising but still limited. The American Brachytherapy Society published guidelines on the use of brachytherapy for

breast cancer, which emphasized the importance of patient selection, careful treatment planning, and use of DVHs and dose homogeneity index.[76] Nevertheless, brachytherapy has several disadvantages compared with external-beam RT, most importantly its invasiveness. Also, if LDR brachytherapy is delivered, the patient has the additional requirement of an isolation room during treatment delivery. Moreover, long-term cosmetic results are not yet available, and the risk of fibrosis and induration at the implant site remains a concern, especially because it can become quite difficult to routinely examine the treated breast.[65,77,78]

External-Beam Techniques. An external-beam approach is likely to be more acceptable to the patient, to be more widely reproducible, to generate improved dose homogeneity, and to result in better cosmetic results compared with brachytherapy techniques. Additionally, it can be made available at any institution with a linear accelerator facility and spare the health care costs of an extra surgical procedure and several days of hospitalization (in the case of LDR brachytherapy).

The first and only randomized trial of partial-breast external-beam radiation versus whole-breast radiation is the Christie Hospital Breast Conservation trial, a trial of 708 patients that included tumors ≤ 4 cm in size with infiltrating ductal and lobular histologies.[79] After lumpectomy, patients were randomized to undergo RT to the tumor bed only (limited-field [LF] group) or to the whole breast and regional nodes (wide-field [WF] group). No systemic therapy was given in either arm. Results of this trial at 8-year actuarial follow-up (median follow-up, 65 months) suggest that the histologic type of the original breast cancer affected local control. In fact, for infiltrating ductal carcinoma, the actuarial breast recurrence rate was 15% for LF radiation versus 11% for WF radiation, whereas for infiltrating lobular carcinoma, the recurrence rates were 34% for LF radiation and 8% for WF radiation. Moreover, in patients with extensive ductal carcinoma in situ, high recurrence rates of 21% (LF group) and 14% (WF group) were also noted. Lumpectomy with LF radiation was feasible; however, the study identified potential patients at higher risk for local recurrence when treated by PBI.

Formenti et al pilot-tested a phase I feasibility study of hypofractionated conformal external-beam RT to the tumor bed in selected postmenopausal women with T1 breast cancers.[80] The rationale for the study was based on the assumption that a few large fractions can be safely delivered to breast cancers provided that the target volume is sufficiently small and the radiation technique assures maximum sparing of the surrounding normal tissue. Using the radiobiologic linear-quadratic cell survival model with an alpha-beta value for breast carcinoma of 4, a dose of 30 Gy in 5 fractions of 6 Gy per fraction over 10 days was found radiobiologically equivalent to a standard dose of 60 Gy in 30 fractions of 2 Gy. The biologic equivalent dose for late breast tissue complications (including desquamation, fibrosis, erythema, and telangiectasia) was less than or equivalent to that of the standard 60 Gy fractionation. The treatment was found to be feasible in 9 of 10 consecutive patients. At a minimum follow-up of 3 years, there were no recurrences and the patients had "good to excellent" cosmetic results. The technique used was derived from a radiosurgical model of delivering external-beam radiation by multiple noncoplanar fields directed toward the tumor bed while sparing as much of the normal tissue as possible.[81] Immobilization of the patient in prone position on a dedicated breast board allowed the breast tissue to freely fall through an opening in the board and reduced to a minimum the motion of the target caused by breathing.

Based on the initial pilot study, a phase I/II study funded by a grant from the Department of Defense (DAMD 17-01-1-0345) is currently ongoing. Currently, 47 of 99 planned patients have been accrued to the study, which consists of a regimen of hypofractionated PBI, 30 Gy in 5 fractions over 10 days.[82] The volume of breast tissue irradiated is the surgical cavity, which is defined at planning computed tomography as the area of postoperative architectural distortion, in conjunction with information derived from mammographic and pathologic findings (Figure 2B). Forty-six of the 47 patients completed treatment with only mild acute toxicity (grade I/II skin toxicity). One patient refused further treatment after 2 fractions with no acute toxicities, but discontinued for personal reasons. At a median follow-up of 17 months (range, 1-39 months), no local recurrences have occurred as of yet. Whereas, in the initial report, 1 of 10 patients could not be treated via the original fractionated radiosurgery-like technique because of the proximity of the lesion to the chest wall. In the next series of 47 patients, the predominant treatment technique was a pair of parallel-opposed mini-tangents.

Baglan et al also piloted a phase I/II study of accelerated PBI in 9 patients.[83] Their technique and dose fractionation differed from that used by Formenti et al in that they treated patients in supine position using an active breathing control method to account for breast movement related to respiratory excursion. Additionally, the model of dose fractionation appeared to be extrapolated from the brachytherapy dose fractionation schedules of 34 Gy in 10 fractions b.i.d. over 5 days in 5 patients, followed by 38.5 Gy in 10 b.i.d. fractions over 5 days in the remaining 4 patients. The technique appeared to be feasible and well tolerated.

Finally, intraoperative RT using a linear accelerator electron beam has been investigated by the European Institute of Oncology at the University of Milan, Italy, which uses a linear accelerator with a robotic arm in an operating room, which delivers electron beams of varying energies: 3, 5, 7, and 9 MeV. The radiation beam is collimated using a Perspex tube.[84] A pilot phase I trial tested different single radiation doses from 10 to 21 Gy after initial quadrantectomy with 1-2 cm clear margins and initial results estimated that a single 21-Gy fraction is radiobiologically equivalent to 60 Gy in 30 fractions in terms of tumor control. However, the initial results of 101 patients were reported with a short median follow-up of 8 months (range, 1-17 months) and concern remains about the effect of such a large single dose on long-term complications, including fibrosis, telangiectasia, and fat necrosis. Advantages of the technique are the even dose distribution achieved by electron-beam RT compared with brachytherapy and the rapidity and potential cost effectiveness of a single treatment.

Research on Genetic Determinants of Long-Term Toxicity

One of the concerns of using larger doses per fraction for breast RT is the potential adverse effects on cosmesis caused by RT-induced fibrosis and skin telangiectasia.[46,48] Current-

ly, no established markers are available for integration to routine practice to predict which group of patients will develop long-term complications. However, in the future, the recognition of genetic predispositions to these complications will enable the exclusion of high-risk carriers from the trials of accelerated/hypofractionated radiation. In other words, similar to the impact of pharmacogenomics in medical oncology, the field of radiation genomics is also rapidly emerging, permitting identification of individuals with genetic predisposition to inferior repair of the damage caused by ionizing radiation. For instance, relevant genetic polymorphisms have started to emerge, including transforming growth factor (TGF)–β1 single-nucleotide polymorphism[85] and mutations of the ataxia telangiectasia mutated (ATM) gene,[86] which have been associated with individuals who were found to have moderate to severe long-term RT-induced complications.

Quarmby et al investigated whether TGF-β1 single-nucleotide polymorphisms were associated with the susceptibility of patients with breast cancer to severe radiation-induced normal tissue damage.[85] They performed polymerase chain reaction–restriction fragment length polymorphism assays for TGF-β1 gene polymorphisms on DNA obtained from 103 patients with breast cancer who received RT. The G-800A, C-509T, T+869C, and G+915C polymorphic sites were examined, and genotype and allele frequencies of 2 subgroups of patients were calculated and compared. The investigators found that the less-prevalent –509T and +869C alleles were significantly associated with a subgroup of patients who developed severe radiation-induced normal tissue fibrosis (n = 15) compared with those who did not (n = 88; odds ratio = 3.4 and $P = 0.0036$; odds ratio = 2.37 and $P = 0.035$, respectively). Furthermore, patients with the –509TT or +869CC genotypes were 7-15 times more likely to develop severe fibrosis. These findings imply a role for the –509T and +869C alleles in the biologic mechanisms underlying susceptibility to radiation-induced fibrosis.

Ianuzzi et al showed a significant correlation between ATM gene status and the development of grade 3/4 subcutaneous late effects in breast cancer by using denaturing high-performance liquid chromatography, a powerful technique in detecting missense mutations and small deletions and insertions.[86] All 3 patients who manifested grade 3/4 subcutaneous late sequelae possessed 2 ATM genes, whereas only 3 of the 43 patients (7%) who did not develop this form of severe toxicity harbored an ATM gene ($P = 0.001$). In contrast, none of the 3 ATM gene carriers who had a single mutation developed a severe subcutaneous reaction.

The future may hold even greater capacity to tailor RT dose–volume fractionation schemes. If fibrosis-associated polymorphic sites in other genes could be identified, it may be possible to detect fibrosis-prone individuals with greater certainty before RT.

Conclusion

Most novel approaches to postoperative RT as part of BCT have included accelerated breast irradiation (ABI). Accelerated breast irradiation to the whole breast or partial breast remains a research approach, as level 1 evidence is currently unavailable to prove its equivalence to standard postoperative RT. Many unresolved issues remain, including optimal patient selection, optimal determination of treatment volume, the ideal dose-fractionation schedule, and total dose. One of the limitations of the external-beam techniques, especially when IMRT is used, is that the integral dose to the remaining breast tissue is higher with increasing number of fields. In addition, for women undergoing partial-breast RT, practically no information exists regarding potential salvage of recurrences after ABI. Finally, the best sequencing pattern with chemotherapy and the ability to perform salvage therapy after ABI also need to be established. However, because of its potential high impact on the care of most patients with breast cancer, ABI should be a research priority in this disease.

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HYPO-FRACTIONATED PARTIAL BREAST RADIATION AFTER BREAST – CONSERVING SURGERY: PRELIMINARY CLINICAL RESULTS AND DOSE VOLUME HISTOGRAM (DVH) ANALYSIS

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ABSTRACT

The current trial tests a regimen of conformal hypo-fractionated radiotherapy directed to the original tumor bed with margins in a selected subset of postmenopausal women with breast cancer with a very low risk of local recurrence elsewhere in the breast. We are reporting the feasibility results and Dose Volume Histogram (DVH) analysis of the first 47 patients accrued. After CT planning is conducted in the prone position, the breast tissue and tumor bed are contoured on a 3D planning system and a 1.5-2 cm margin added to determine the Planning Target Volume (PTV). A plan is generated to treat the PTV to a minimum of 90% of the prescription dose, 6 Gy per fraction delivered in 5 fractions over ten days to a total dose of 30 Gy. All 47 patients have tolerated the treatment very well. DVH varied based on the position of the original tumor bed and the size of the breast. In most cases it was possible to successfully plan and treat a quadrant of the breast with parallel opposed tangent fields without exceeding 50% of the dose to the 50% of the breast volume. Accrual continues as planned, to a total of 99 patients.

BACKGROUND

A new patient population is emerging because of screening mammography, composed of post-menopausal women with non-palpable tumors, measuring less than 2 cm, (T1).[1-3] The optimal management of these patients remains to be defined.[4-6] Since local recurrence of T1 lesions tend to occur within the original breast quadrant[7] it is rational to investigate the role of partial breast radiation. Moreover, the reduction of the volume to irradiate has opened the opportunity to accelerate treatment.[8,9] After completing a pilot study to explore feasibility[10,11] we developed a phase I-II study to test a regimen of conformal hypo-fractionated radiotherapy (5 fractions in 2 weeks) offered to selected post-menopausal who have refused conventional adjuvant radiation (30 fractions in 6 weeks).

OBJECTIVES

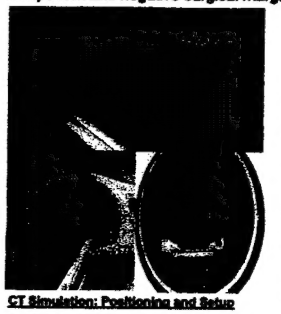
1. To determine the **feasibility** of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers
2. To explore the **efficacy** of this approach compared to historical local control rates achieved by standard post-operative radiation
3. To assess the role of circulating **TGF-β1** pre-treatment as a marker for fibrosis

METHODS

Patients eligibility

Clinical: post-menopausal patients with newly diagnosed non-palpable T1 stage invasive breast cancer. Patients had to decline standard radiation therapy (6 weeks) to be eligible

Pathological Eligibility: pT1 tumor, pN0 or sentinel node negative or N0 clinically if the tumor is <1 cm in size, estrogen receptor positive, lack of an extensive intraductal component and negative surgical margins (<5 mm)



CT Simulation: Positioning and Setup

The patient is positioned prone on a dedicated table that allows target breast tissue to fall freely through an opening

Intent

To treat 25% of breast tissue, while sparing the lung, heart and as much remaining breast tissue as feasible

Dose

6 Gy/fraction prescribed to the 95% isodose surface

5 fractions over ten days, M,W,F and M,W (total dose = 30Gy)

Technique:

Positioning: CT planning prone, on a dedicated table

Target Definition: Classic breast tangent borders established while supine to define whole ipsilateral breast volume (IBV). Excised tumor bed (CTV) delineation based upon density changes seen on planning CT scan.

PTV: tumor bed + 1.5-2 cm margin contoured on a 3D planning system

DVH: ipsilateral breast, lung and heart contoured at CT

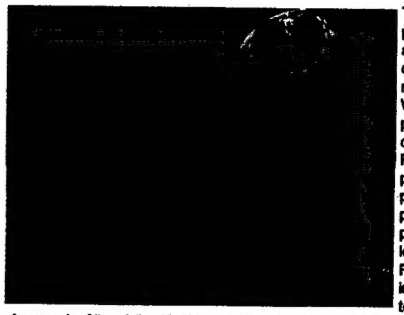
RESULTS

Patient Characteristics

Since June 2000, forty-seven postmenopausal women were accrued to the study (median age 67.5 years, range: 51 to 88). The median tumor diameter was 1 cm (range 0.2-1.9 cm). Forty-six of the 47 patients completed treatment and are available for follow-up. One patient refused further treatment after 2 fractions. She reported no acute toxicities but she refused to continue for personal reasons.

The median length of follow-up of the 47 patients is 17 months (range: 1-39 months). All patients showed no evidence of local recurrence in the index breast. One patient developed metastatic squamous cell carcinoma of the lung with mediastinal, paraspinal and osseous metastases, 2 ½ months after completion of radiation therapy. Her condition rapidly deteriorated and she expired 3 months after completion of the protocol treatment.

Treatment Planning Results



An example of the relationship of tumor bed to PTV is demonstrated in the panels above with the tumor bed (red wash), PTV (blue), heart (pink), lung (light green). The PTV represents a 1.5 cm margin on the tumor bed. The lower panels represent the Digital Reconstructed Radiographs, RAO and LPO portals for a left sided breast cancer.

The predominant technique for treatment was a pair of parallel-opposed tangents. This arrangement assured good coverage given the constraints imposed by the PTV and its relationship to the table.

We found heterogeneity of DVH based on the position of the original tumor bed and the size of the breast.

Four patients were treated in the supine position (as accepted protocol deviations), two patients were unable to tolerate lying in the prone position secondary to paraplegia and two patients, the position of the tumor bed was located very lateral and better treated supine

For the entire group the volume of breast tissue included by the 95% isodose ranged from 10% to 45%.

In all patients, the intent to treat <50% of the breast receiving <50% of the dose was respected.

However, in 12 of the 47 patients, in order to successfully treat the PTV, greater than 50% of the ipsilateral breast volume received >50% of the dose.

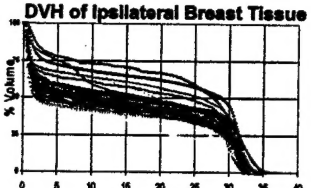
This was largely dependent on the size of the surgical cavity and its location in comparison to the index breast.

Volume DVH Summary

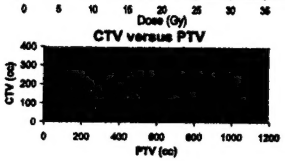
	Median	Range
IBV (cc)	1034	256-3468
CTV (cc)	35	7- 380
PTV (cc)	192	57 - 1118
CTV/IBV (%)	4	1- 22
PTV/IBV (%)	20	9- 55
CTV/PTV (%)	20	6- 46
V100 (%)	25	10- 45
V50 (%)	46	23- 75

IBV: ipsilateral breast volume CTV: tumor bed; clinical target volume PTV: planning target volume V100: volume covered by the 100% isodose surface V50: volume covered by the 50% isodose surface

DVH of Ipsilateral Breast Tissue



CTV versus PTV



As expected, the CTV correlated with the PTV

Acute Toxicity

The most common acute toxicity was grade 1-2 erythema (21 of 47 patients) occurring in the treatment portal, and fatigue (11 patients) usually manifesting in the second week, 2 patients reported Grade I-2 nausea. Two patients developed Grade 1 dry desquamation, 1 patient with Grade I breast edema. Six patients had induration at the surgical scar, predating radiation therapy,

Late Toxicity

There were 33 patients who have 6 months of follow-up or greater. Preliminary assessment of late toxicity, included 12 patients who developed 17 events, including grade I-2 induration (5 patients), fibrosis (1 patient) , breast edema (2 patients), telangiectasia (5 patients), hyperpigmentation (4 patients).

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total # pts	Total # of pts treated
Acute Radiation Dermatitis	18	3	0	0	21	47
Late Skin Toxicity	10	2	0	0	12	33

Preliminary Assessment of Cosmesis

With a median follow-up of 17 months, preliminary cosmetic grading by the treating physician was "good to excellent" in 24 of 26 patients, "fair" in 2 patients at baseline, which was not changed by the addition of radiation therapy.

CONCLUSIONS

- Preliminary data (47 patients) suggest that this approach is feasible and well tolerated
- In all patients the intent to treat was respected but in 12/47 to successfully treat the PTV, 50% of the ipsilateral breast volume received > 50% of the dose
- Constraints include the location of the tumor bed and the ratio of the PTV / volume of ipsilateral breast. Alterations in the table design might improve the current dosimetric findings
- Longer follow-up is required to to measure efficacy, cosmesis and to assess the role of circulating TGF-β1 pre-treatment as a marker for post-treatment fibrosis

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